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Brief Report

Prolonged Uninterrupted Sitting Increases Fatigue in Type 2 Diabetes

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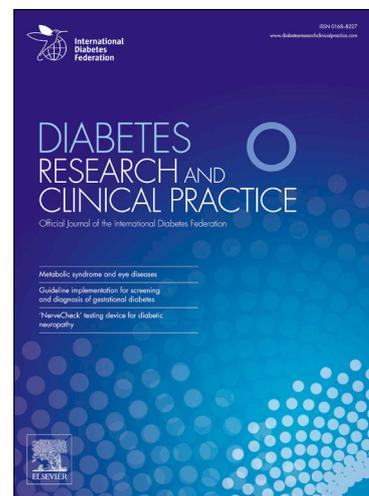
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Manuscript Title:

Prolonged Uninterrupted Sitting Increases Fatigue in Type 2 Diabetes

Running title: Prolonged sitting and fatigue in type 2 diabetes**Authors and Affiliations:**Paddy C. Dempsey^{1,2}, David W. Dunstan^{1,4,5,6,7}, Robyn N. Larsen¹, Gavin W. Lambert^{1,2}, Bronwyn A. Kingwell¹, Neville Owen^{1,2,3,4}¹ Baker Heart and Diabetes Institute, Melbourne, VIC, Australia² Centre for Urban Transitions & Iverson Health Innovation Research Institute, Swinburne University of Technology, Melbourne, VIC, Australia³ Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia⁴ Institute of Physical Activity and Nutrition Research, School of Exercise and Nutrition Sciences, Deakin University, Melbourne, VIC, Australia⁵ Mary MacKillop Institute of Health Research, Australian Catholic University, Melbourne, VIC, Australia⁶ School of Public Health, The University of Queensland, Brisbane, QLD, Australia⁷ School of Sport Science, Exercise and Health, The University of Western Australia, Perth, WA, Australia

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E paddy.dempsey@baker.edu.auThis manuscript is submitted as a **Research Brief** for *Diabetes Research and Clinical Practice*, which requires a word count limit of 1,000 words and 20 references.

50 word summary

Fatigue is a prevalent, costly and disabling clinical complaint among those with type 2 diabetes. In a randomized crossover trial, prolonged uninterrupted sitting increased fatigue by 29% relative to days when sitting was regularly interrupted by brief activity-breaks. This may have implications for diabetes-related quality of life, occupational productivity and self-care.

Keywords: Type 2 Diabetes; Fatigue; Sitting; Sedentary Behaviour; Physical activity; Self-Care Behavior; Patient Self-Management; Health care delivery; Psychological aspects

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INTRODUCTION

The 2016 American Diabetes Association's Position Statement on exercise and type 2 diabetes (T2D) has included specific recommendations to reduce and interrupt prolonged sitting (1). This is based on evidence that high volumes of daily sitting time are associated with poorer cardiometabolic health outcomes (2), and that regular brief interruptions to prolonged sitting time can acutely improve cardiometabolic risk markers in those with T2D (3-5). Further to concerns about cardiometabolic risk, prolonged sitting can lead to increased fatigue (6), which is a pervasive, costly and disabling complaint among those with T2D (7, 8). This may have implications for diabetes-related quality of life and self-care (7, 9, 10). We examined fatigue in those with T2D after a day of prolonged uninterrupted sitting, compared to sitting interrupted by regular brief activity breaks.

METHODS

Study overview

This randomized crossover trial was approved by the Institutional Research Ethics Committee and all participants provided written informed consent. Detailed screening, participant characteristics, and testing procedures have been described previously (3, 4). Twenty-four participants (14 men, 10 women; mean±SD age, 62±6 years; BMI, 33.0±3.4 kg·m⁻²; HbA1c, 7.2±0.7%; eGFR 87±8 mL·min⁻¹·1.73m⁻²; diabetes duration 6.8±5.1 years; 23 taking metformin; 15 taking statins) completed all trial conditions in a randomized order, each separated by 6-14 days. In this context, the "control" conditions were considered as the days where participants were regularly interrupting their sitting with brief bouts of light activity (BREAKS), in comparison to a day of prolonged uninterrupted sitting (SIT). Study personnel were blinded to the condition order until the night prior to the first trial condition, while participants were blinded to trial condition order up until commencement of the second trial visit.

Trial conditions

On the trial days, participants arrived at the laboratory around 7:15 AM after a 12-h fast. Each laboratory condition was 8-h total duration and commenced with a 60-min 'sitting steady-state' period (-1 h to 0 h), after which participants consumed standardized breakfast (0 h) and lunch (3.5 h) meals (see Figure), and began the following experimental protocols after the breakfast meal:

SIT: Participants sat upright in a comfortable chair throughout experimental period, and were instructed to minimize excessive movement, only rising from the chair to attend the lavatory.

BREAKS: Participants completed two trial-conditions on separate days, during which sitting time was interrupted every 30 min (on 12 occasions, totaling 36 min) by either: 3-min bouts of light-intensity walking on a treadmill (3.2 km·h⁻¹ with zero gradient) (LW); or, by 3-min bouts of simple resistance activities (alternating between body weight-resisted half-squats, calf raises, and knee raises with a gluteal contraction, while mimicking a standardized video recording) (SRA).

Participants undertook the respective laboratory condition protocols under direct supervision from research staff. They had access to television, DVDs, books, magazines and internet services during the trial conditions, which were kept consistent between trial conditions.

Physical activity, diet, medications, sleep and other physiological measures

As previously described (4), participants refrained from exercise, alcohol and caffeine from 48 h prior until the morning after each trial condition. Meals were standardized during trial conditions and medications were kept constant. Dietary and accelerometer-derived physical activity data 48 h before each of the respective trial conditions, and anthropometric and biochemical data on the morning of each trial condition, were not significantly different (4). Throughout the trial, sleep quality was assessed each morning using a modified Consensus Sleep Diary (11). Other relevant measures were fasting and postprandial plasma glucose/insulin (4) at 30 min intervals and 22 h continuous glucose monitoring (iPro2; Medtronic, Northridge, CA, USA) (3).

Fatigue Assessment

At -1, 1, 3, 4.5 and 5.5 h, participants completed the Lee Fatigue Scale (12). This tool consists of 18 visual analogue scale items (from 0-100 mm) related to fatigue and energy, with higher scores indicating greater fatigue severity and higher levels of energy (distinct visual analogue scales). It has multiple items to characterize and subjectively quantitate various behavioural manifestations of fatigue and energy levels as they are being experienced, with comparisons between extremes. For example, “not at all” to “extremely” tired, sleepy, fatigued, worn out, energetic, lively, drowsy, exhausted, etc. The Lee Fatigue Scale was chosen as it is relatively short and easy to administer, has well-established validity and internal reliability, with Cronbach’s alpha (α) coefficients for the fatigue and energy subscales between 0.91–0.96 (12).

Statistical analyses

Generalized linear mixed-models with random intercepts examined the differential effects of the experimental conditions on fatigue/energy outcome values using Stata 14 (StataCorp LP). All models met assumptions of linearity and normality of residuals. Statistical significance was set at $P < 0.05$. Time-by-condition interaction and P for linear trend tests were performed to examine changes in fatigue/energy over time. Mean fatigue/energy scores (Figure D-F) were quantified as the mean of all time points after -1 h. All models were adjusted for potential covariates explaining residual outcome variance (age, BMI and gender), including baseline (-1 h) fatigue values, sleep quality and period effects (treatment order). To explore potential physiological determinants of fatigue, Pearson’s pairwise correlation tests examined whether changes in fatigue/energy between trial conditions were correlated with concurrently measured changes in glycemic control/variability (13).

RESULTS

Mean total fatigue and fatigue- and energy-specific scores across each trial condition period are displayed in the Figure. Overall mean fatigue and energy subscale scores were correlated at -0.62. Condition-by-time interaction effects were observed for total fatigue and fatigue-specific scores, but not energy-specific scores relative to baseline (-1 h) fatigue (Figure A-C).

During the SIT condition, both total fatigue and fatigue-specific scores progressively increased across the day relative to baseline, while energy-specific scores progressively decreased (Figure and Table). Conversely, total fatigue and fatigue-specific scores remained relatively unchanged across the day for BREAKS, while energy-specific scores were progressively increased (Figure and Table). Compared to the BREAKS conditions, SIT increased mean total fatigue and fatigue-specific scores by 29-33%, and decreased mean energy-specific scores by 26-27% (D-F; $P < 0.05$). There were no significant correlations between changes in fatigue/energy and changes in glycemic control/variability between trial conditions (data not shown).

DISCUSSION

In adults with T2D, a day of prolonged uninterrupted sitting resulted in progressively increased fatigue, relative to days when sitting time was interrupted by regular brief activity breaks. Increases in fatigue did not occur across the light-walking nor the simple resistance activity break conditions. These findings build on evidence that highlights the detrimental effects of prolonged uninterrupted sitting time on cardiometabolic risk markers in those with T2D (3-5). They are also consistent with two recent experimental studies in adults without T2D, which showed increases in fatigue with prolonged sitting over a day relative to sitting interrupted every 30-60 mins with light-walking breaks (14, 15) or with transitions between sitting and standing (15). While we did not observe significant correlations between hyperglycemia or glucose variability and fatigue, there is evidence both supporting and countering the hypothesis that hyperglycemia and higher glucose variability may be related to adverse mood states and fatigue in those with diabetes (7, 16, 17).

The cross-over design is a strength of this study, since it enhances both the internal validity and reliability of our findings, permits a smaller sample size, and provides control for person-specific factors. Limitations include the self-assessment of fatigue, which may be prone to biases including prior expectations and social desirability, given that it is not possible to blind participants to trial conditions. However, the one-week washout period between trial conditions should have reduced participants' ability to recall their prior VAS scoring – alleviating such biases. Since each trial visit was imposed under controlled laboratory conditions, the examination of a separate/additional “control group” in free-living settings may have served to reduce these biases, and could be considered in future studies. Such a control group would have also provided further insights on the impact of prolonged uninterrupted sitting and/or regular activity breaks on fatigue, relative to a “true” reference comparator, in more real-world settings. Boredom is an established contributor to fatigue, but was countered in our study through various activities (e.g. TV, internet, and reading) performed during sitting periods. However, since boredom was not explicitly measured, its potential impact on the findings cannot be determined. In addition, our findings do not shed light on the distinction between acute and prolonged fatigue (weeks-months), the latter of which has been more directly related to functional impairments in daily functioning for those with T2D (7, 18). Finally, the mediating mechanisms driving increased fatigue during prolonged sitting, and the clinical and longer-term implications, should be elucidated in future research.

In conclusion, a day of prolonged uninterrupted sitting increased fatigue in those with T2D. These increases were not apparent when sitting was interrupted by regular brief activity breaks. In the context of high volumes of daily sitting and the growing proportion of working adults living with T2D, there may be important implications for workplace productivity, self-care regimens (e.g. medications, diet, exercise) and diabetes-related quality of life.

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PCD conceived, designed and conducted the study, analyzed and interpreted the data, and wrote the manuscript. DWD, RNL, GWL, BAK and NO assisted in the concept and design of the study and participated in critical revision of the manuscript for intellectual content. All authors approved the final version of this manuscript. PCD and DWD are the guarantors of this work and, as such, had full access to all the study data and take responsibility for data integrity and accuracy of the data analysis.

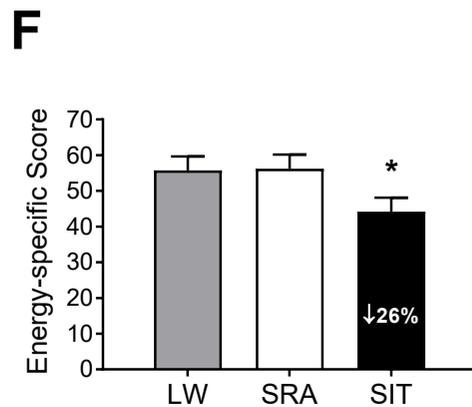
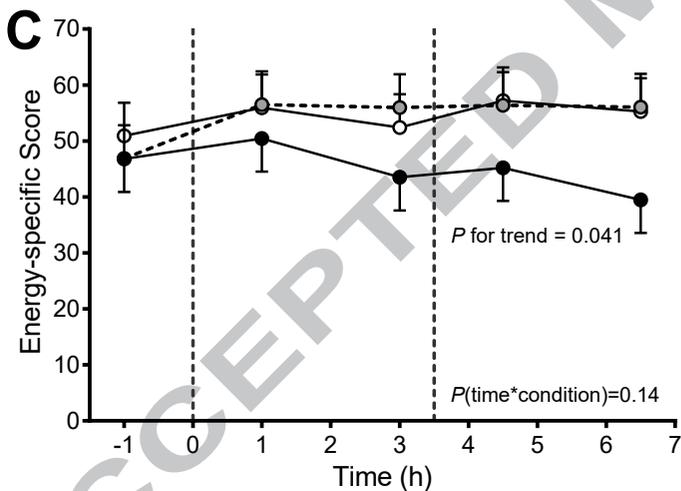
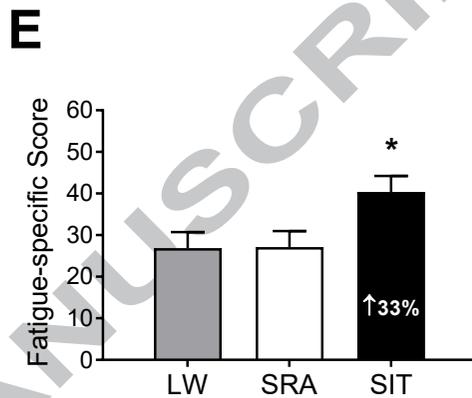
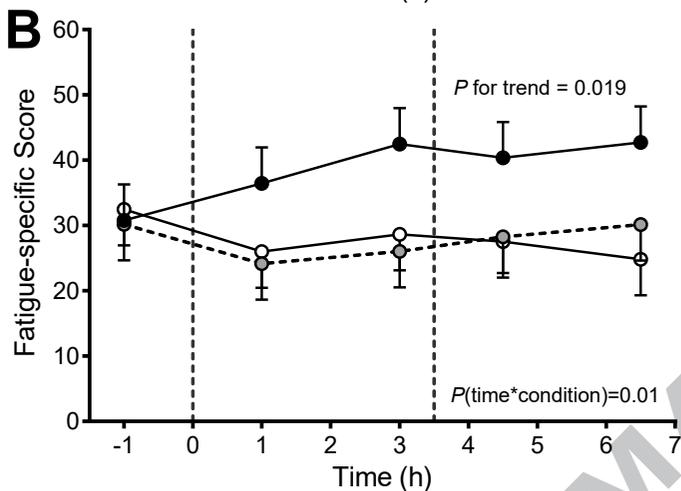
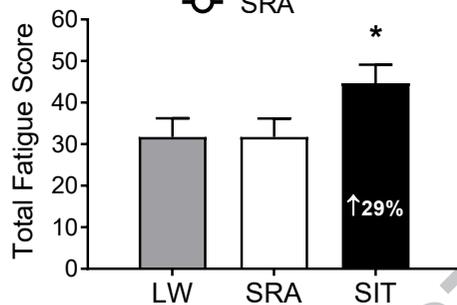
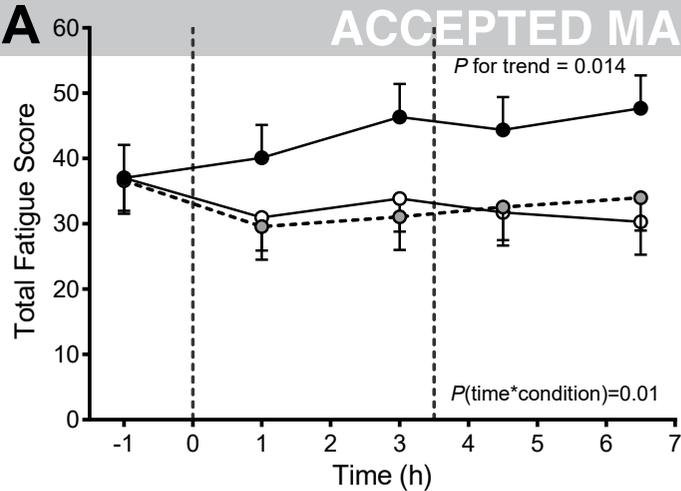
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FIGURE LEGEND

Figure. The effect of prolonged uninterrupted sitting and sitting interrupted with 3-min LW and SRA breaks on fatigue and energy scores (0-100 point scale) over time (A-C) and mean fatigue and energy scores (i.e. averaged values for all time points after -1 h), controlling for baseline (-1 h) fatigue, treatment order, sex, BMI, age and sleep quality (D-F). Vertical dashed lines in panels A-C indicate the timing of the breakfast (0 h) and lunch (3.5 h) meals. Values within the bars (panels D-F) represent the mean percentage change in fatigue/energy scores compared with both LW and SRA. *Difference from LW and SRA ($P<0.05$). See Table for pairwise statistical comparisons over time. Data are mean (95% CI).

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● SIT
○ LW
○ SRA



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Table. Between-condition and within-condition effects on fatigue and energy scores over time.

	Condition	Time point (h)					<i>P</i> for linear trend over time
			-1	1	3	4.5	
Overall Fatigue Composite Score							
Difference between conditions	WALK vs. SIT	NS	-11 [-17, -4]	-15 [-22, -9]	-14 [-20, -7]	-10 [-17, -4]	
	SRA vs. SIT	NS	-9 [-16, -3]	-13 [-19, -6]	-13 [-19, -6]	-17 [-24, -11]	
	SRA vs. WALK	NS	1 [-5, 8]	3 [-4, 9]	-1 [-7, 6]	-4 [-10, 3]	
Difference relative to time point -1 h (baseline)	SIT	REF	3 [-3, 10]	9 [3, 16]	7 [1, 14]	11 [4, 17]	0.014
	WALK	REF	-7 [-14, -1]	-6 [-13, 1]	-4 [-11, 2]	-3 [-10, 4]	0.681
	SRA	REF	-6 [-13, 0]	-3 [-10, 3]	-5 [-12, 1]	-7 [-13, 0]	0.154
Fatigue-specific Subcategory Score							
Difference between conditions	WALK vs. SIT	NS	-12 [-19, -5]	-16 [-23, -10]	-13 [-19, -6]	-10 [-17, -3]	
	SRA vs. SIT	NS	-10 [-17, -4]	-14 [-21, -7]	-13 [-20, -6]	-18 [-25, -11]	
	SRA vs. WALK	NS	2 [-5, 9]	3 [-4, 10]	-1 [-8, 6]	-5 [-12, 2]	
Difference relative to time point -1 h (baseline)	SIT	REF	6 [-1, 13]	12 [5, 19]	10 [3, 16]	12 [5, 19]	0.019
	WALK	REF	-7 [-14, 0]	-5 [-12, 2]	-3 [-9, 4]	-1 [-8, 6]	0.284
	SRA	REF	-5 [-12, 2]	-2 [-9, 5]	-3 [-10, 4]	-6 [-13, 1]	0.164
Energy-specific Subcategory Score							
Difference between conditions	WALK vs. SIT	NS	6 [-2, 14]	12 [5, 20]	17 [9, 24]	11 [3, 19]	
	SRA vs. SIT	NS	6 [-2, 13]	9 [1, 17]	12 [4, 20]	16 [8, 24]	
	SRA vs. WALK	NS	-1 [-8, 7]	-4 [-11, 4]	1 [-7, 9]	-1 [-9, 7]	
Difference relative to time point -1 h (baseline)	SIT	REF	4 [-4, 11]	-3 [-11, 4]	-2 [-9, 6]	-7 [-15, 0]	0.041
	WALK	REF	10 [2, 17]	9 [1, 17]	10 [2, 17]	9 [2, 17]	0.214
	SRA	REF	9 [1, 17]	6 [-2, 13]	10 [3, 18]	8 [1, 16]	0.268

Data are mean (95% CI). Bold typeface indicates significance at $P < 0.05$ between conditions per time point or relative to the reference (REF) category. NS, indicates baseline (-1 h) time point not significantly different between conditions ($P > 0.05$).